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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/623,533	09/05/2000	Dominique P. Bridon	REDC-1510USA	3921

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EXAMINER	
PARKIN, JEFFREY S	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 06/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/623,533	BRIDON ET AL.	
	Examiner	Art Unit	
	Jeffrey S. Parkin, Ph.D.	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *03* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,4,6,19-21,31-43 and 52-56* is/are pending in the application.

4a) Of the above claim(s) *32-35,40-43,54 and 56* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4,6,19-21,31,36-39,52,53 and 55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Serial No.: 09/623,533
Applicants: Bridon, D.P., *et al.*

Docket No.: REDC-151USA
Filing Date: 09/05/00

Response to Amendment

Status of the Claims

Acknowledgement is hereby made of receipt and entry of the amendment submitted 26 January, 2004. Claims 1, 3, 4, 6, 19-21, 31-43, and 52-56 are pending in the instant application. Claims 32-35, 40-43, 54, and 56 stand withdrawn from further consideration as being directed towards a nonelected invention (refer to 37 C.F.R. § 1.142(b) and M.P.E.P. § 821.03). Claims 1, 3, 4, 6, 19-21, 31, 36-39, 52, 53, and 55 are currently under consideration. Applicants again traverse the restriction requirement, this time arguing that the conjugated peptides are related to the modified peptides as intermediates and final product. The basis for the lack of unity finding was clearly set forth in the Office action mailed 14 June, 2002. Applicants' arguments were adequately addressed in the subsequent Office action mailed 22 October, 2002. As previously set forth, the claimed invention clearly lacks unity of invention. Each of the products in the identified groups (i.e., modified peptides, protein-peptide conjugates) have different structural and functional characteristics. The modified peptides may be employed in the absence of further chemical modifications (i.e., without conjugating them to blood comoponents) or the peptides may be conjugated to sundry chemical partners (i.e., fluorescent moities, biotin, small polypeptides to prepare immunogenic compositions, high moleclular weight carriers such as PEG, or larger proteins). Thus, contrary to applicants' assertion, a special technical feature is not present.

35 U.S.C. § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3, 4, 6, 19-21, 31, 36-39, 52, 53, and 55 stand rejected under 35 U.S.C. § 112, first paragraph, because the specification does not reasonably enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. Applicants argue that the claims have been amended to address the concerns raised in the last Office action. Contrary to applicants' assertion, the claims remain broadly directed toward modified antiviral peptides "comprising" a peptide with one of the recited SEQ ID NOS.:. The claims have not been amended, as previously suggested[1], to reflect the true nature of the invention (i.e., modified DP-178 peptides, amino or carboxyl truncations thereof, or natural variants thereof, with maleimido-groups). Thus, the amendments set forth do not address the deficiencies in the claimed subject matter.

The legal considerations that govern enablement determinations pertaining to undue experimentation have been clearly set forth. *Enzo Biochem, Inc.*, 52 U.S.P.Q.2d 1129 (C.A.F.C. 1999). *In re Wands*, 8 U.S.P.Q.2d 1400 (C.A.F.C. 1988). *Ex parte Forman* 230 U.S.P.Q. 546 (PTO Bd. Pat. App. Int., 1986). The courts concluded that several factual inquiries should be considered when making such assessments including the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the

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[1] Suggested claim language that would obviate the rejection was set forth in the Office action mailed 25 September, 2003 (i.e., An isolated and purified chemically modified anti-viral peptide consisting of a DP-178 peptide that has been modified to contain a succinimidyl or maleimido group at the _, wherein said peptide displays a reduced susceptibility to protease degradation as compared to the unmodified DP-178 peptide ... and said peptide consists of an amino acid

invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims. *In re Rainer*, 52 C.C.P.A. 1593, 347 F.2d 574, 146 U.S.P.Q. 218 (1965).

The disclosure fails to provide adequate guidance pertaining to a number of these considerations as follows:

1) The breadth of the claims is excessive and fails to receive adequate support in the disclosure. Contrary to applicants' assertion, the claim language remains "open" (a peptide comprising) and only requires that one of the specified core sequences be present. However, the claims clearly allow for the addition of one or more amino acids to either or both the amino and carboxy termini. The flanking sequences may consist of any length and any combination of amino acids. However, the disclosure only describes specific DP-178 peptides without any discussion of flanking regions.

2) The disclosure fails to provide adequate support concerning those adjacent amino acids that will result in retention of the antiviral activity of the peptide of interest. As noted below in item 3, retroviral envelope glycoproteins are large and complex. There are many factors that contribute to the proper folding and processing of the envelope glycoprotein. The same constraints apply to larger molecules comprising the recited core sequences. The disclosure fails to provide any structural guidance pertaining to the amino acid composition of adjacent regions. Thus, the skilled artisan cannot predict which adjacent or flanking amino acid sequences will result in retention of the desired properties.

3) The state-of-the-art concerning the effects of flanking amino acid sequences on peptide structure and function is often unpredictable. It has been well-documented in the art that the addition of flanking sequences can have an unpredictable influence on the immunological, virological, and biochemical properties of

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sequence selected from the group consisting of ...).

any given peptide (Sanders *et al.*, 2002; Yang *et al.*, 2000; Kwong *et al.*, 2000; Wang *et al.*, 1995). For instance, Sanders and colleagues (2002) reported that the instability of the HIV-1 Env comlex presents problems when attempting to express the native complex as a recombinant protein. Yang and associates noted earlier the lability of the Env complex has hindered the production of recombinant forms of the Env. The invention is predicated upon the inhibition of an active fusion conformation that is generated during virion-cell surface receptor binding and entry. Thus, the peptide of interest needs to be able to interact with the complex in a highly specific manner in order to effectively inhibit viral replication. However, it seems extremely unlikely that larger homologous or heterologous sequences attached to the termini would produce a peptide with the same specificity and antiviral activity. The skilled artisan would reasonably expect steric hindrance to prevent the polypeptide of interest from binding to the complex. Moreover, the disclosure fails to provide sufficient guidance pertaining to those additional flanking sequences that can be included without abrogating antiviral activity.

4) Moreover, the first paragraph of 35 U.S.C. § 112 requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification (refer to M.P.E.P. §§ 706.03(n) and 796.03(z)). *In re Fisher*, 427 F.2d 833, 839, 166 U.S.P.Q. 18, 24 (C.C.P.A. 1970). *In re Vaeck*, 20 U.S.P.Q.2d 1438 (C.A.F.C. 1991). Particularly where the subject matter is directed towards arts where the results are unpredictable. *In re Sol*, 1938 CD 723; 497 O.G. 546. This is because in arts such as chemistry it is not obvious from the disclosure of one species, what other species will work. *In re Dreshfield* 1940 CD 351; 518 O.G. 255. Applicants have clearly failed to meet their burden under the statute.

Accordingly, when all the aforementioned factors are considered *in toto*, it would clearly required undue experimentation from the

skilled artisan to practice the claimed invention.

35 U.S.C. § 103(a)

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103(a).

Claims 1, 3, 4, 6, 19-21, 31, 36-39, 52, 53, and 55 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Bolognesi *et al.* (1996) in view of Krantz *et al.* (2000). Bolognesi and colleagues disclose HIV-1 antiviral peptides derived from amino acids 607-642 of the transmembrane envelope glycoprotein (gp41) (see pages 1, 7, 24-30). Specifically, a peptide designated DP-178/T20 was described, as well as, various amino- and carboxyl-

terminal truncations of this region (see pages 26-27, Tables I and Ia). This teaching does not disclose peptides that have been modified to incorporate a succinimidyl- or maleimido-containing group, which is capable of reacting with amino groups, hydroxyl groups, or thiol groups, to facilitate peptide cross-linking to blood components.

Krantz and associates disclose the preparation of tripeptide compounds comprising chemically reactive intermediates (i.e., succinimidyl- or maleimido-containing groups). These intermediates are capable of forming covalent linkages with reactive groups on blood components (see col. 3, lines 34-52; col. 5, lines 9-22, 27-56; col. 6, lines 31-36). These polypeptide derivatives display extended half-lives when conjugated to blood components thereby lowering their IC_{50}, as compared to the unconjugated parent compound (see col. 5, lines 57-65). The inventors provide a detailed discussion about conjugation chemistry and suitable reactive groups including, succinimidyl- and maleimido-containing groups (see col. 5, lines 9-22, 27-56; col. 6, lines 31-36; cols. 6/7, bridging paragraph; col. 7, lines 9-19). It was further reported that there are several advantages to employing maleimido-containing peptides including the following: 1) the modified peptides are generally quite stable in aqueous solutions; 2) protective groups are not required to prevent self-reactivity; 3) increased peptide stability permits additional purification steps required for *in vivo* administration; and 4) increased chemical stability provides a longer shelf-life (see cols. 6/7, bridging paragraph). Specifically, the inventors reported (see col. 2, lines 40-52) that "conjugated renin inhibitors thereby have extended lifetimes in the bloodstream, as compared to the unconjugated parent drug, and are, therefore, capable of maintaining renin activity for extended periods of time as compared to the unconjugated parent drug." This teaching does not disclose peptides derived from the DP-178 region of HIV-1 gp41.

However, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to modify the antiviral peptides described by Bolognesi *et al.* (1996), to include succinimidyl- or maleimido-containing reactive groups, as described by Krantz *et al.* (2000), that are capable of forming stable covalent bonds with blood components. One of ordinary skill in the art would have been motivated to make said chemical modifications because Krantz *et al.* (2000) clearly disclose that said modifications have several advantages including the following: 1) increasing peptide stability and the circulating half-life in aqueous solutions; 2) protective groups are not required to prevent self-reactivity; 3) increased peptide stability permits additional purification steps required for *in vivo* administration; and, 4) increased chemical stability provides a longer shelf-life. Thus, both the motivation and a reasonable expectation of success were present in the prior art.

Correspondence

Any inquiry concerning this communication should be directed to Jeffrey S. Parkin, Ph.D., whose telephone number is (571) 272-0908. The examiner can normally be reached Monday through Thursday from 9:30 AM to 7:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner are unsuccessful, the examiner's supervisors, Laurie Scheiner or James Housel, can be reached at (571) 272-0910 or (571) 272-0902, respectively. Direct general inquiries to the Technology Center 1600 receptionist at (571) 272-1600.

Formal communications may be submitted through the official facsimile number which is (703) 872-9306. Hand-carried formal communications should be directed toward the customer window located in Crystal Plaza Two, 2011 South Clark Place, Arlington, VA. Applicants are directed toward the O.G. Notice for further

guidance. 1280 O.G. 681. Informal communications may be submitted to the Examiner's RightFAX account at (571) 273-0908.

Respectfully,

Jeffrey S. Parkin, Ph.D.
Patent Examiner
Art Unit 1648

10 May, 2004